Management of Diabetic Patients with Kidney Diseases

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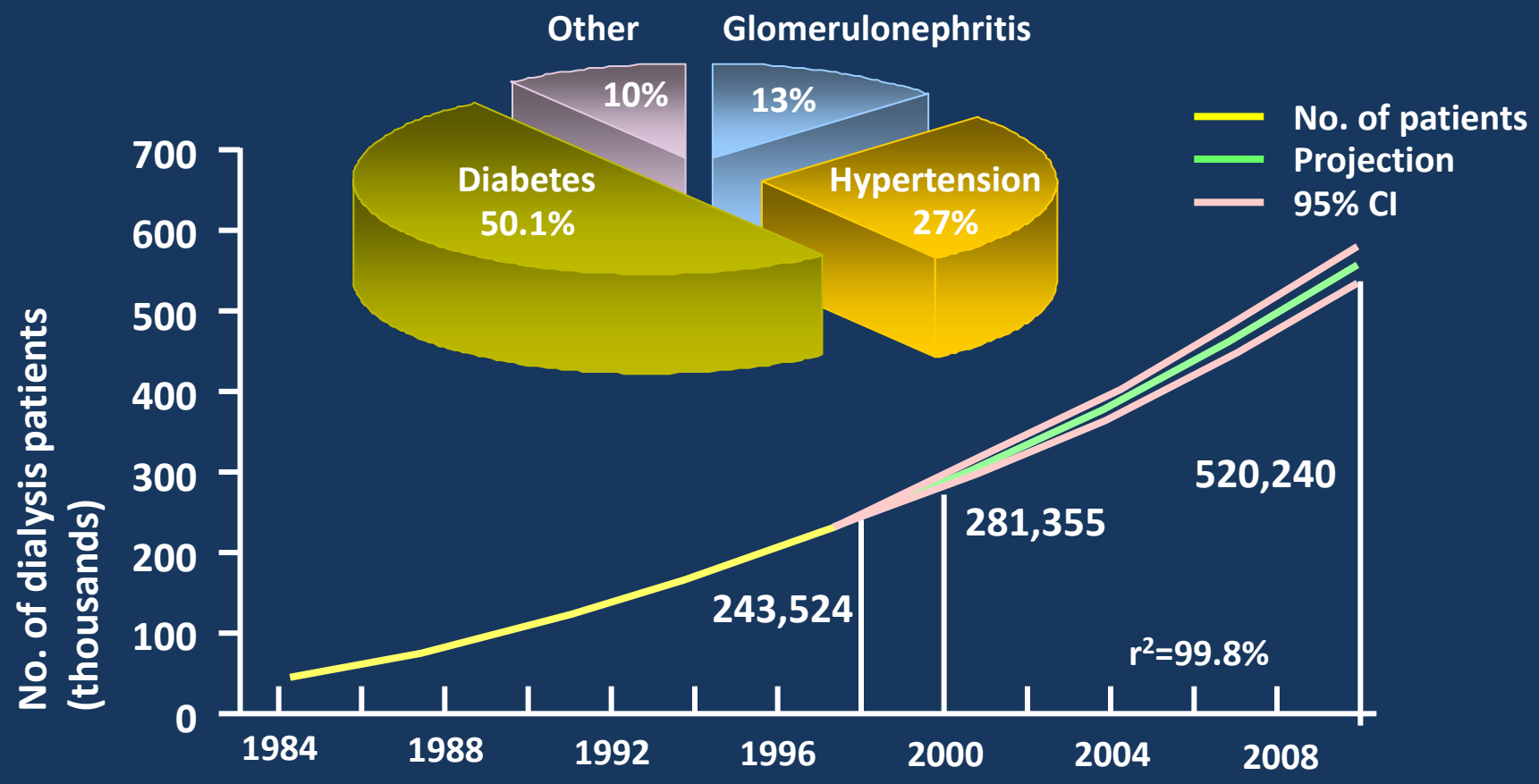
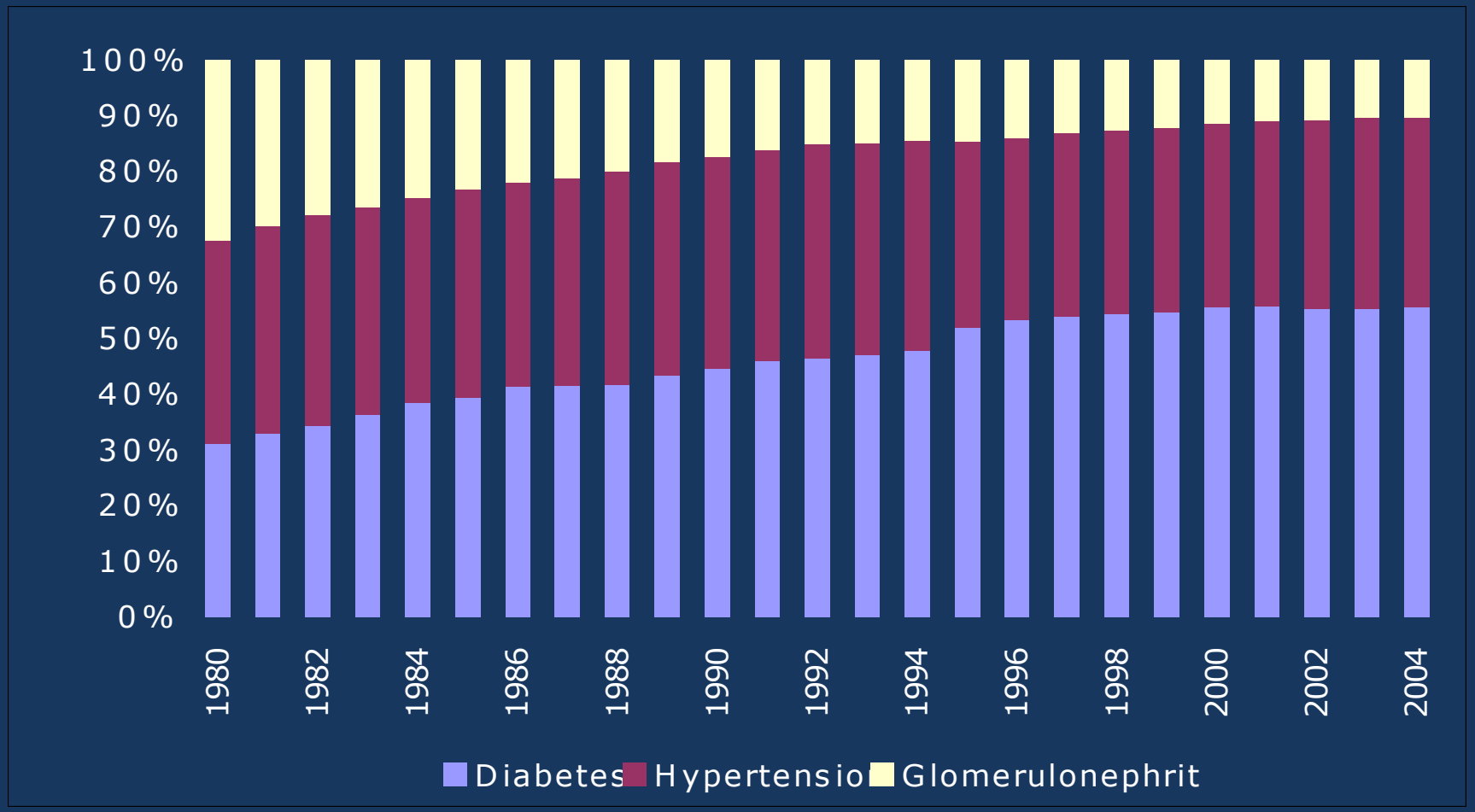
Diabetes: The Most Common Cause of ESRD

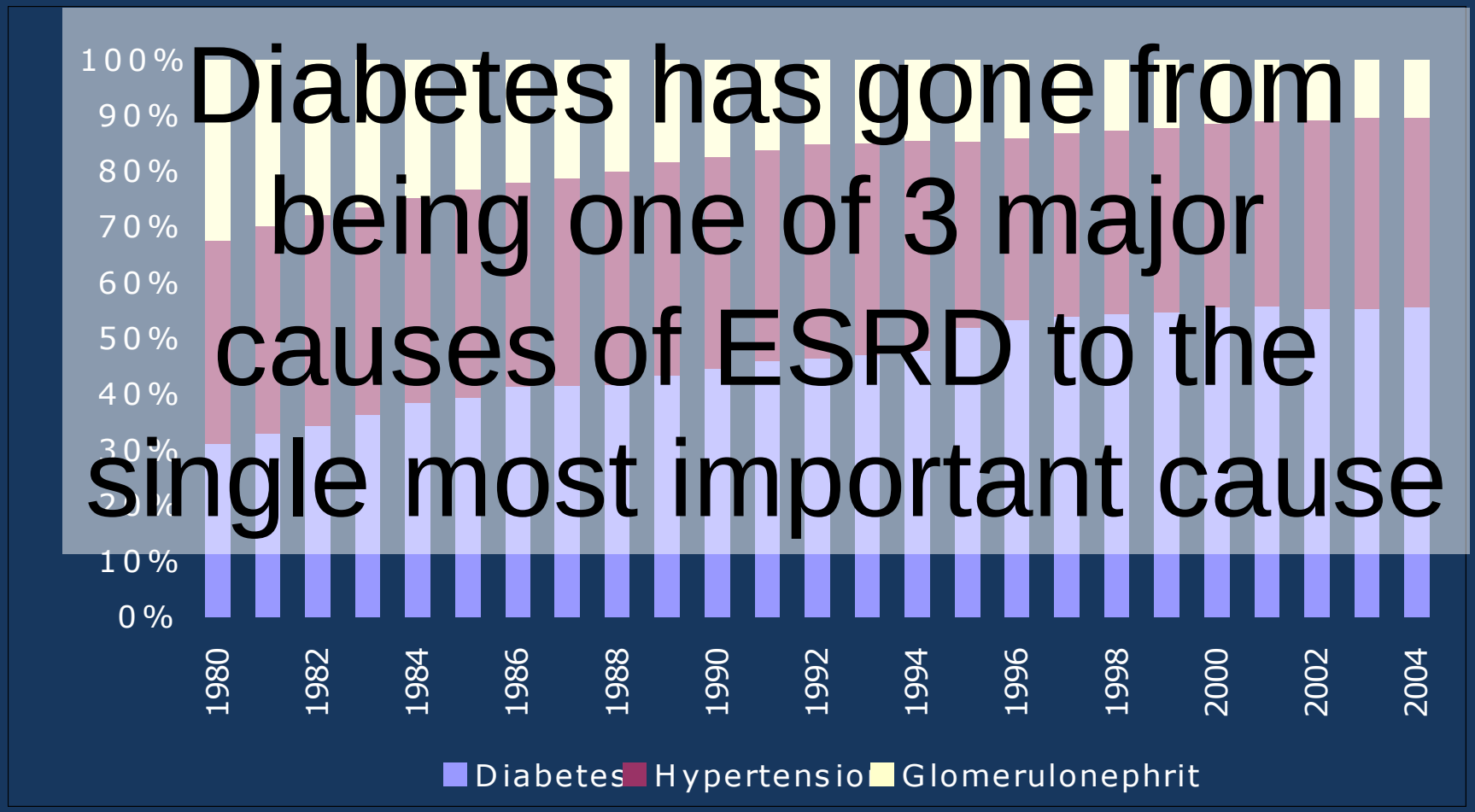
Primary Diagnosis for Patients Who Start Dialysis



United States Renal Data System. Annual data report. 2000.

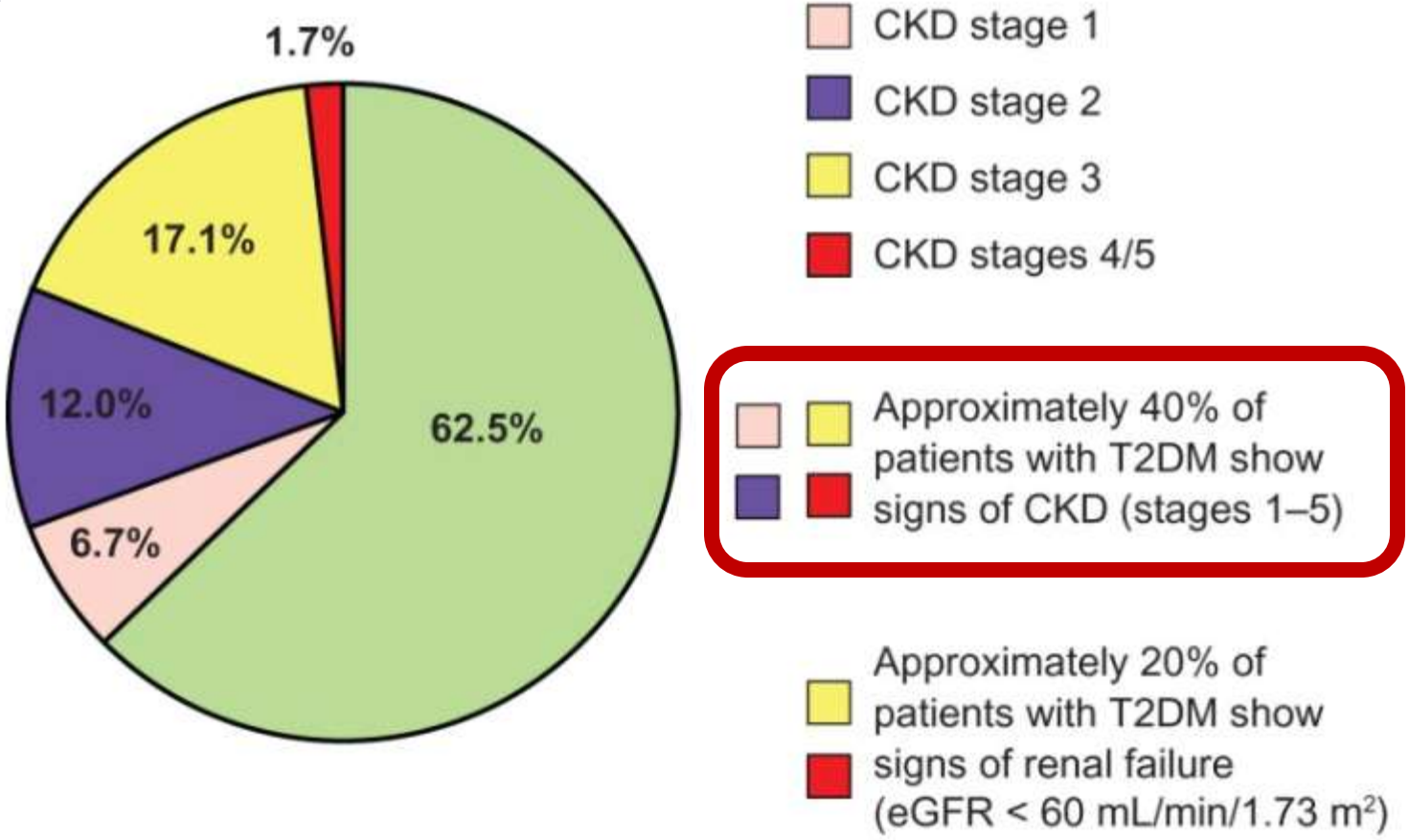
Incidence of CRF





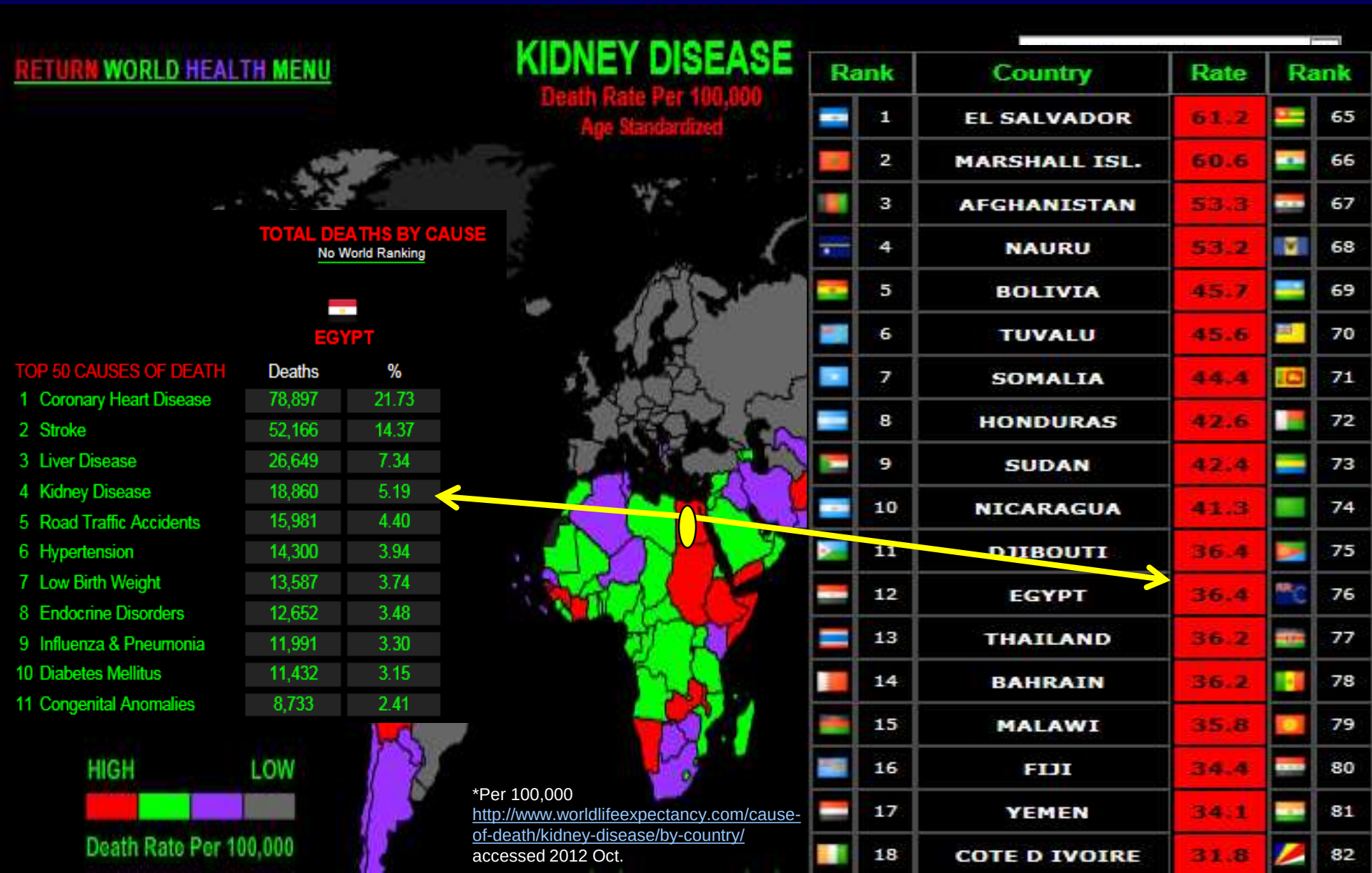
Diabetes has gone from being one of 3 major causes of ESRD to the single most important cause

Renal Dysfunction Is Common in Patients with Type 2 Diabetes



Russo E, et al. Diabetes Metab Syndr Obes. 2013; 6: 161–170.

Death Rate of Kidney Diseases in Egypt is 36.4* with About 5.19% of all Deaths



*Per 100,000
http://www.worldlifeexpectancy.com/cause-of-death/kidney-disease/by-country/
accessed 2012 Oct.

National Kidney Foundation™

Definition of CKD

Structural or functional abnormalities of the kidneys for ≥3 months, as manifested by either:

1. Kidney damage, with or without decreased GFR, as defined by
    - pathologic abnormalities
    - markers of kidney damage, including abnormalities in the composition of the blood or urine or abnormalities in imaging tests
2. GFR <60 ml/min/1.73 m^2, with or without kidney damage

Prevalence of CKD and Estimated Number of Adults with CKD in the US (NHANES 88-94)

Stage	Description	GFR (ml/min/1.73 m^2)	Prevalence*	
			N (1000s)	%
1	Kidney Damage with Normal or ↑ GFR	≥ 90	5,900	3.3
2	Kidney Damage with Mild ↓ GFR	60-89	5,300	3.0
3	Moderate ↓ GFR	30-59	7,600	4.3
4	Severe ↓ GFR	15-29	400	0.2
5	Kidney Failure	< 15 or Dialysis	300	0.1

*Stages 1-4 from NHANES III (1988-1994). Population of 177 million with age ≥20. Stage 5 from USRDS (1998), includes approximately 230,000 patients treated by dialysis, and assuming 70,000 additional patients not on dialysis. GFR estimated from serum creatinine using MDRD Study equation based on age, gender, race and calibration for serum creatinine. For Stage 1 and 2, kidney damage estimated by spot albumin-to-creatinine ratio ≥17 mg/g in men or ≥25 mg/g in women in two measurements.

Definition and Prevalence of CKD

13.1% (one in eight) of the adult population has CKD

= 27,000,000

- Definition of CKD
  - Kidney damage (abnormalities in blood, urine or imaging studies)

  or

  - eGFR < 60 mL/min/m^2

    for ≥ 3 months

Diabetic Nephropathy

- A microvascular complication of diabetes marked by
  - albuminuria and
  - a deteriorating course from normal to ESRD.

Definitions of Abnormalities in Albumin Excretion

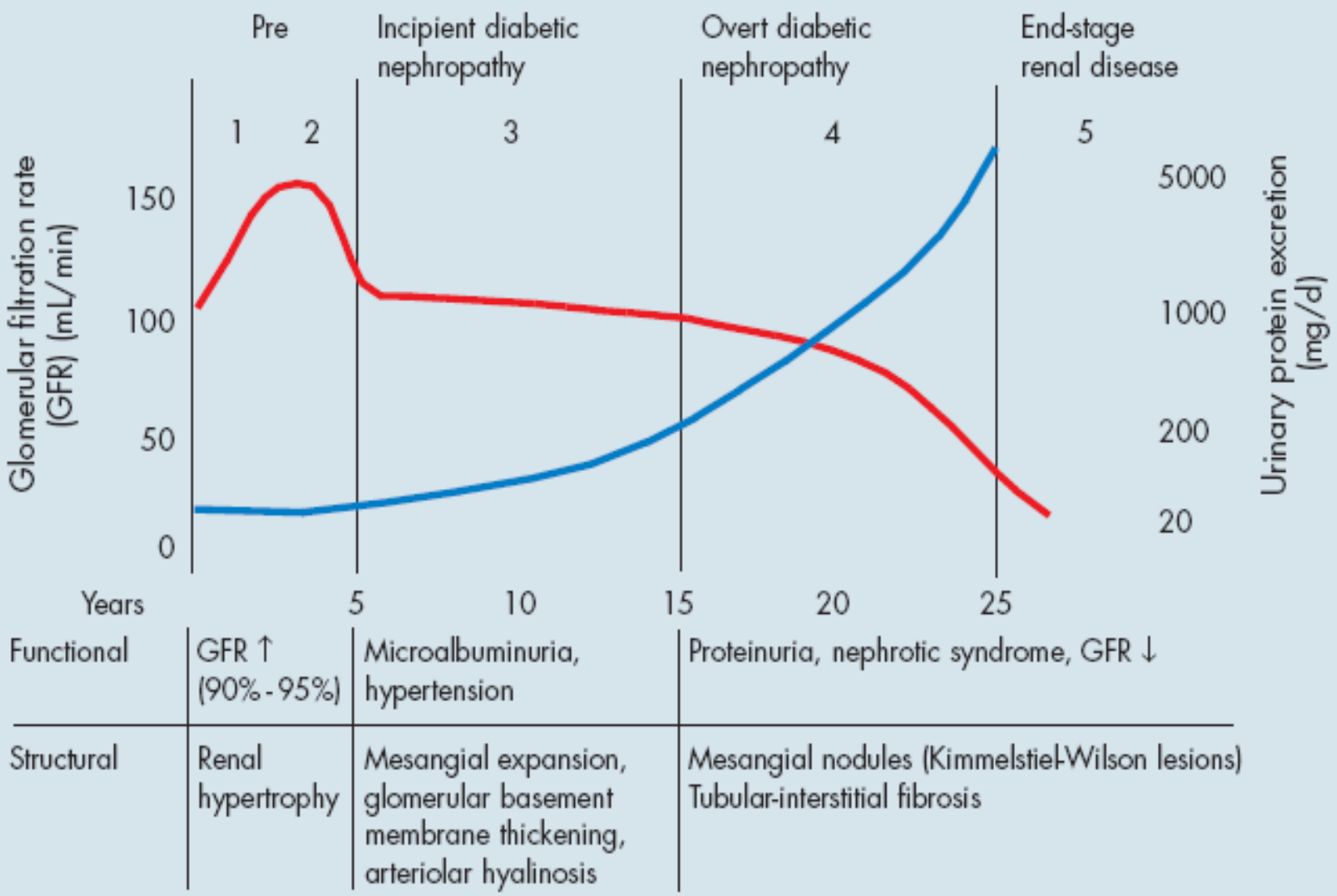
Category	Spot collection (µg/mg creatinine)
Normal	<30
Microalbuminuria	30-299
Macroalbuminuria (clinical)	≥300

ADA. VI. Prevention, Management of Complications. *Diabetes Care* 2011;34(suppl 1):S34. Table 13.

Risk factors for diabetic nephropathy

- **Poor glycemic control**
- **Poor hypertension management**
- Smoking

- Family history of hypertension (first-degree relative)
- Genetic predisposition (family clustering)
- Intrauterine diabetes exposure
- Type 1 diabetes with onset in teenage years
- Male sex



From Vora JP et al. *Comprehensive Clinical Nephrology*. 2000.[53] Used with permission.

Management of DM In patients with Kidney disease

Prevention and treatment of diabetic nephropathy

- Primary prevention: ↓ Progression from normo- to microalbuminuria
- Secondary prevention: ↓ Progression from microalbuminuria to DN
- Tertiary prevention: ↓ Progression from DN to ESRD

primary prevention of development of diabetic nephropathy

- Strict diabetic control
- RAAS Blokade
- Lipid lowering drugs?
- Low protein diet?

Lower A1C Reduces Incidence of Complications

A1C	DCCT 9 → 7%	Kumamoto 9 → 7%	UKPDS 8 → 7%
Retinopathy	63%	69%	17-21%
Nephropathy	54%	70%	24-33%
Neuropathy	60%	–	–
Macrovascular disease	41%*	–	16%*

* Not statistically significant.

Diabetes Control and Complications Trial (DCCT) Research Group. *N Engl J Med.* 1993;329:977-86.
Ohkubo Y et al. *Diabetes Res Clin Pract.* 1995;28:103-17.
UK Prospective Diabetes Study Group (UKPDS) 33. *Lancet.* 1998;352:837-53.

secondary prevention of development of diabetic nephropathy

- Strict diabetic control
- Antihypertensive treatment
  - RAAS Blokade
- Multifactorial intervention

tertiary prevention of progression to ESRF

- Antihypertensive treatment
- Blood glucose control
- Low protein diet ?
- Lipid lowering drugs ?
- Stop smoking ?

Management of DM In patients with Kidney disease

ADA Recommendations: Nephropathy Screening

Assess urine albumin excretion annually (B)

- In type 1 diabetic patients with diabetes duration of ≥5 years
- In all type 2 diabetic patients at diagnosis

Measure serum creatinine at least annually (E)

- In all adults with diabetes regardless of degree of urine albumin excretion
- Serum creatinine should be used to estimate GFR and stage level of chronic kidney disease, if present

American Diabetes Association.

ADA. VI. Prevention, Management of Complications. *Diabetes Care* 2013;36(suppl 1):S34.

Management of CKD in Diabetes (1)

GFR	Recommended
All patients	Yearly measurement of creatinine, urinary albumin excretion, potassium
45-60	Referral to nephrology if possibility for non diabetic kidney disease exists
	Consider dose adjustment of medications
	Monitor eGFR every 6 months
	Monitor electrolytes, bicarbonate, hemoglobin, calcium, phosphorus, parathyroid hormone at least yearly
	Assure vitamin D sufficiency
	Consider bone density testing
	Referral for dietary counselling

American Diabetes Association.

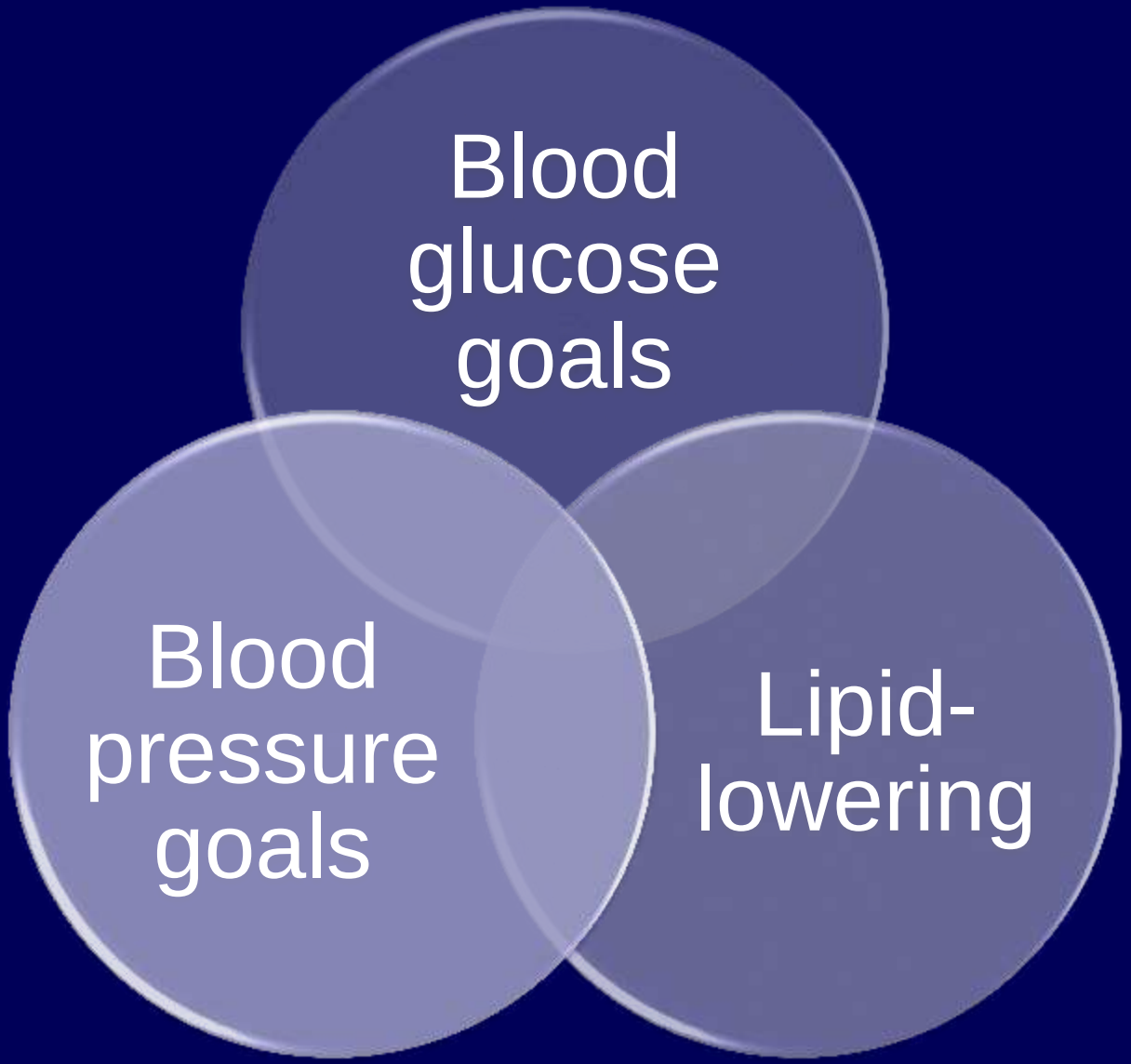
ADA. VI. Prevention, Management of Complications. *Diabetes Care* 2013;36(suppl 1):S37; Table 13; Adapted from http://www.kidney.org/professionals/KDOQI/guideline_diabetes/

Management of CKD in Diabetes (2)

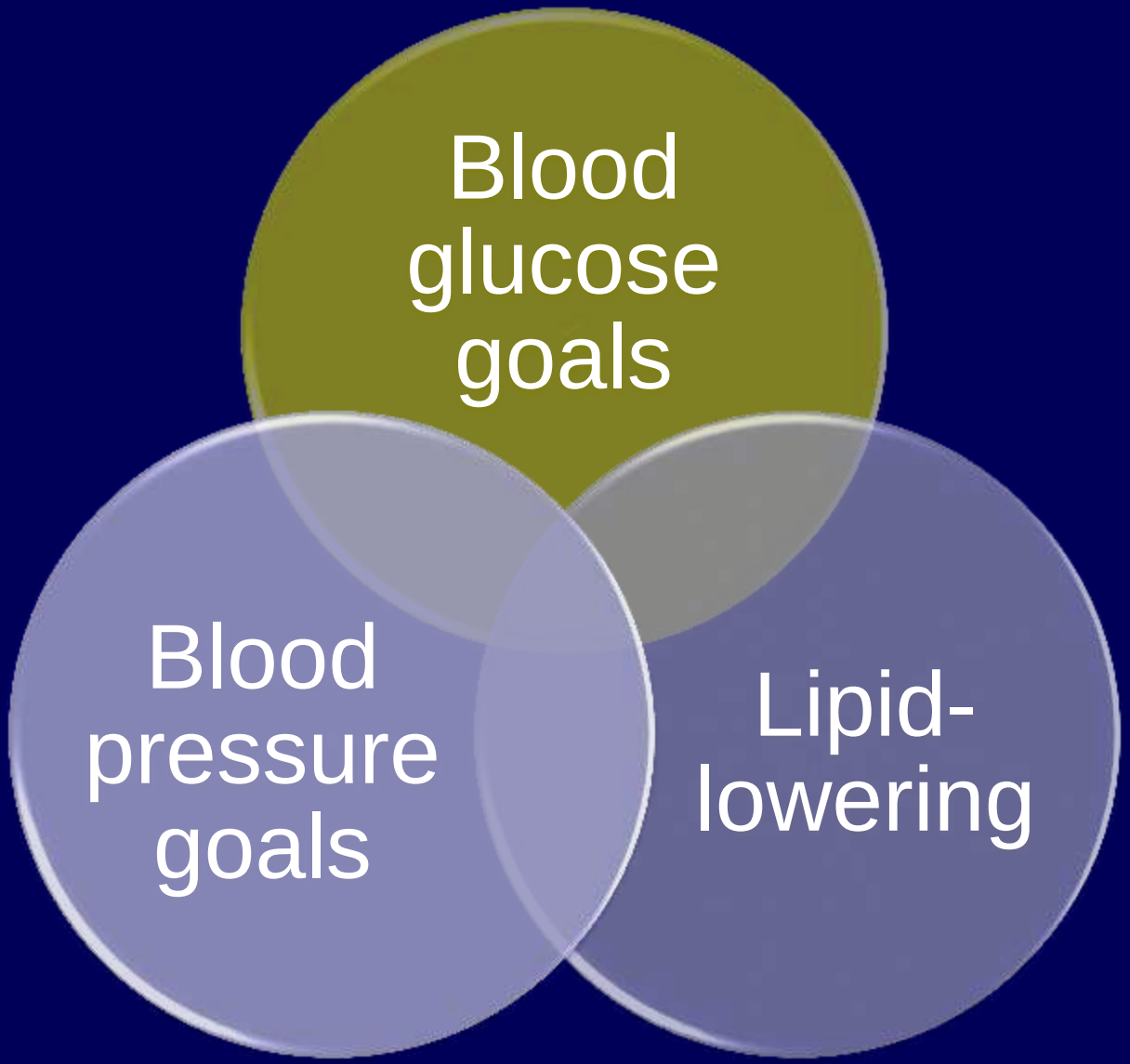
GFR	Recommended
30-44	Monitor eGFR every 3 months
	Monitor electrolytes, bicarbonate, calcium, phosphorus, parathyroid hormone, hemoglobin, albumin weight every 3–6 months
	Consider need for dose adjustment of medications
<30	Referral to nephrologist

ADA. VI. Prevention, Management of Complications. *Diabetes Care* 2013;36(suppl 1):S37; Table 13; Adapted from http://www.kidney.org/professionals/KDOQI/guideline_diabetes/

Effective Management:



Effective Management:



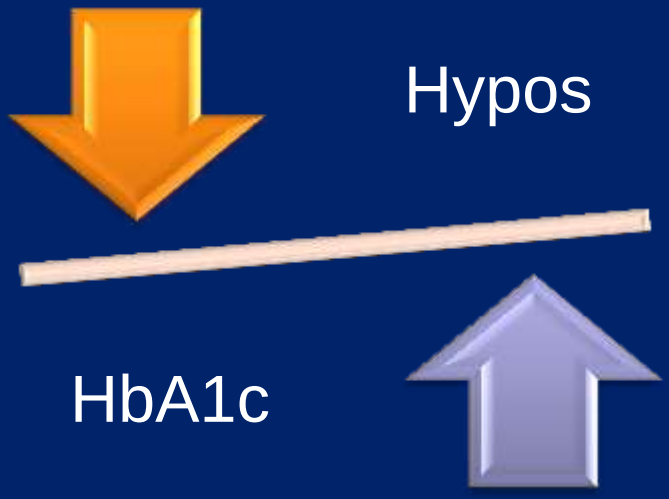
Standard Care and Target Values Proposed for CKD Patients with Diabetes Mellitus

Parameter	CKD 3/4	CKD 5 and 5D
Metabolic control		
glycosylated hemoglobin	> 6.5 – 7.5 g%	> 7.0-8.0 g%
preferred agents		
Blood pressure	130/80 mmHg	
preferred agents	ACE/ARB's	np/Betablockers
Lipid treatment		
LDL cholesterol	<100 mg/dl	np
preferred agents	statins	np/ns
Anemia treatment		
Hemoglobin level	11.0 – 12.0 g/dl	11.0 – 12.0 g/dl (avoid >13)
preferred agents	iron/ESA	ESA/iron
Vitamin D supplements	Vit. D3/1.25-OHD	1.25 OHD/Vit. D3
Supportive treatment		
Smoking cessation	++	np
hypoglyemia awareness	++	+++
Lowdose aspirin	++	+/np
Exercise (daily/weekly)	+	+
Foot care	+++	+++
Prevention of falls	+	+++

National Kidney Foundation
KDOQI

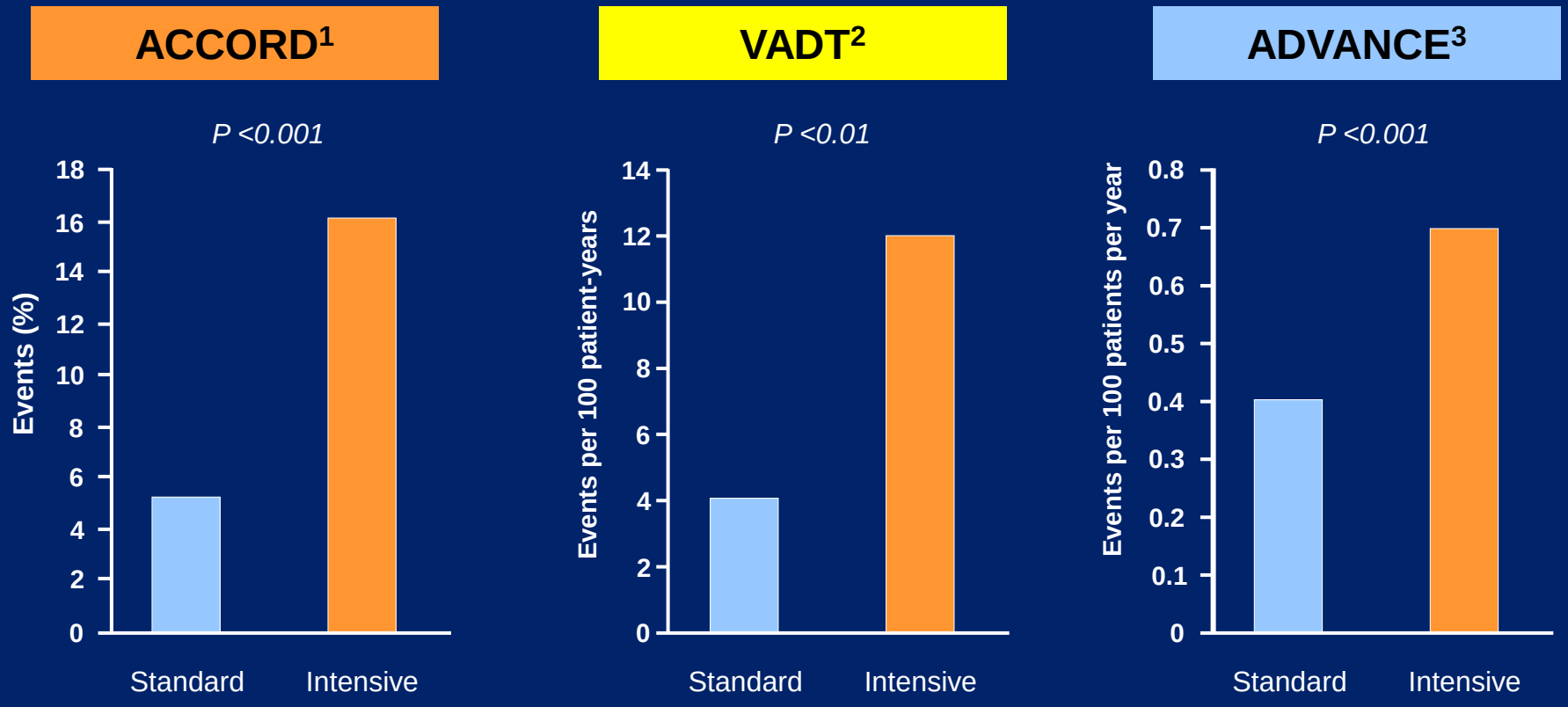
Hypoglycaemia

“The major limiting factor to achieving intensive glycaemic control for people with type 2 diabetes”



Briscoe VJ, *et al. Clin Diab* 2006;24:115-121.

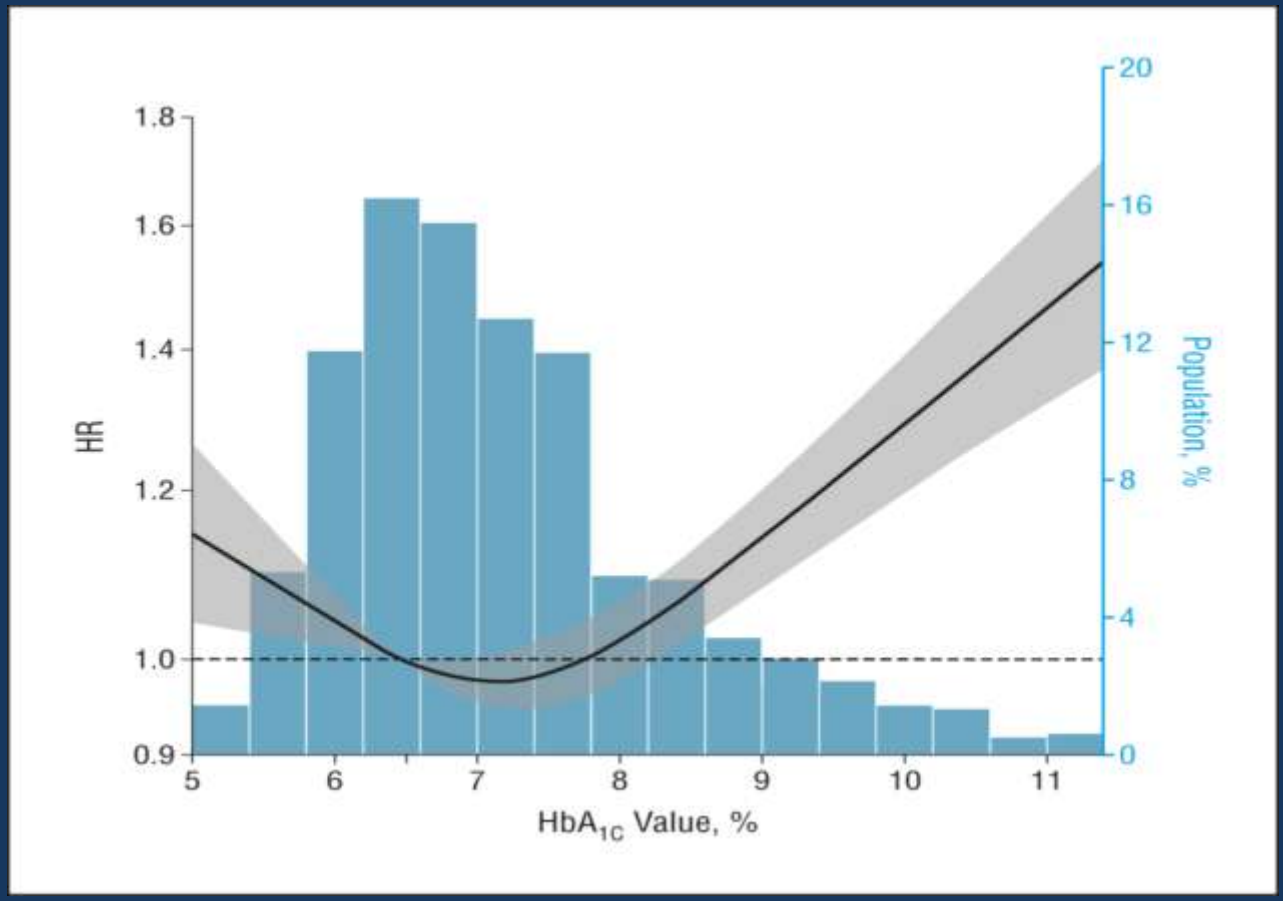
Treat to target increases the risk of hypoglycemia in ACCORD, VADT and ADVANCE



1. ACCORD Study Group. N Engl J Med. 2008;358:2545–2559
2. Duckworth W, et al. N Engl J Med. 2009;360:129–139
3. ADVANCE Collaborative Group. N Engl J Med. 2008;358:2560–2572

2011: Association Between Glycemic Control and Adverse Outcomes in People With Diabetes Mellitus and Chronic Kidney Disease

U-shaped relationship between HbA1c level & risk of death, with deaths increasing significantly for HbA1c levels below 6.5% and above 8% over nearly 4 years of follow-up.



Shurraw S et al, Arch Intern Med. 2011;171(21):1920-1927.

Therapeutic options for blood glucose-lowering

Intervention	Expected decrease in HbA_{1C} with monotherapy (%)	Advantages	Disadvantages
Lifestyle to decrease weight and increase activity	1.0-2.0	Broad benefits	Insufficient for most within first year
Metformin	1.0-2.0	Weight neutral	GI side effects, contraindicated with renal insufficiency
Insulin	1.5-3.5	No dose limit, rapidly effective, improved lipid profile	One to four injections daily, monitoring, weight gain, hypoglycemia,
Sulfonylurea	1.0-2.0	Rapidly effective	Weight gain, hypoglycemia (especially with glibenclamide or chlorpropamide)
TZDs	0.5-1.4	Improved lipid profile (pioglitazone), potential decrease in MI (pioglitazone)	Fluid retention, CHF, weight gain, bone fractures, expensive, potential increase in MI (rosiglitazone)
GLP-1 agonist	0.5-1.0	Weight loss	Two injections daily, frequent GI side effects, long-term safety not established, expensive
Other therapy			
α-Glucosidase inhibitor	0.5-0.8	Weight neutral	Frequent GI side effects, three times/day dosing, expensive
Glinide	0.5-1.5[1]	Rapidly effective	Weight gain, three times/day dosing, hypoglycemia, expensive
Pramlintide	0.5-1.0	Weight loss	Three injections daily, frequent GI side effects, long-term safety not established, expensive
DPP-4 inhibitor	0.5-0.8	Weight neutral	Long-term safety not established, expensive

1.Repaglinide more effective in lowering HbA_{1C} than nateglinide. CHF, congestive heart failure; GI, gastrointestinal; MI, myocardial infarction.

Nathan DM, *et al. Diabetes Care* 2009;32 193-203.

KDOQI Diabetes Guideline 2012: Metformin

- Metformin does not cause hypoglycemia.
- Lactic acidosis is a rare and serious side effect of metformin, which can occur when toxic levels of metformin accumulate.
- Metformin is cleared by the kidneys, thus its use in CKD is restricted.
- Given its marked clinical benefit, restriction of metformin use based on the creatinine cutoffs provided by the FDA ≤1.5mg/dl in man and ≤1.4mg/dl in women , or a GFR cutoff of ‹ 60 mL/min/1.73 m2, has been called into question.
- A recent review proposed that metformin use be reevaluated when GFR is ‹45 mL/min/1.73 m2 and stopped when ‹ 30 mL/min/1.73 m2; this advice was adopted by the British National Formulary.

National Kidney Foundation. KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 update. *Am J Kidney Dis*. 2012;60(5):850-886.

KDOQI Diabetes Guideline 2012: Thiazolidinediones

- Pioglitazone does not lead to hypoglycemia, is metabolized by the liver, and thus can be used in CKD.

- However, fluid retention is a major limiting side effect and they should not be used in advanced heart failure and CKD.

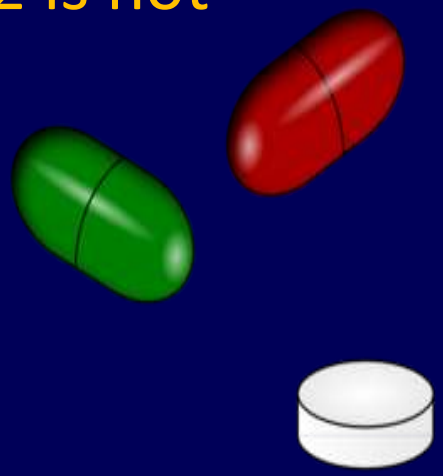
- They have been linked with increased fracture rates and bone loss, thus the appropriate use in patients with underlying bone disease (such as renal osteodystrophy) needs to be considered.

National Kidney Foundation. KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 update. *Am J Kidney Dis*. 2012;60(5):850-886.

KDOQI Diabetes Guideline: 2012 Update Acarbose

- Acarbose, a disaccharidase inhibitor, is only minimally absorbed, but with reduced kidney function, serum levels of the drug and its metabolites increase significantly.

- Although no adverse effects have been reported, its use in patients with a ‹GFR26 mL/min/ 1.73 m2 is not recommended.



National Kidney Foundation. KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 update. *Am J Kidney Dis*. 2012;60(5):850-886.

KDOQI Diabetes Guideline 2012: Injectable Incretin Mimetics GLPa

- Exenatide is excreted by the kidneys, and its clearance is reduced by 36% with a GFR of 45 mL/min/1.73 m2 and by 64% with a GFR of 30 mL/min/1.73 m2.62 Therefore**, exenatide is not recommended for use with a GFR ‹ 30 mL/min/1.73 m2.**

- Furthermore, exenatide has been associated with acute kidney injury or acceleration of CKD progression in case reports.

- Liraglutide, there are few data on long term use and the manufacturer recommends avoiding this medicine when GFR is ‹ 60 mL/min/1.73 m2

National Kidney Foundation. KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 update. *Am J Kidney Dis*. 2012;60(5):850-886.

KDOQI Diabetes Guideline 2012: Sulfonylureas

- Progressive falls in kidney function result in **decreased clearances of the sulfonylureas** or their active metabolites, necessitating a decrease in drug dosing to avoid hypoglycemia

National Kidney Foundation. KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 update. *Am J Kidney Dis*. 2012;60(5):850-886.

Use of conventional antidiabetic medications in T2DM with CKD

Table 2 Use of conventional antidiabetic drugs in type 2 diabetic patients with chronic kidney disease

	eGFR >60 mL/min	eGFR 30–59 mL/min	eGFR <30 mL/min	Dialysis
Insulin	✓	✓	✓ dose reduction	✓ dose reduction
Metformin	✓	✓ caution	⊘	⊘
Sulfonylureas	✓	caution	caution	⊘
Metiglinides	✓	✓ caution	caution	⊘
Thiazolidinediones	✓	✓ caution	✓ caution	✓ caution
Alpha-glucosidase inhibitors	✓	✓	⊘	⊘

Note: ⊘, use not allowed.

Abbreviation: eGFR, estimated glomerular filtration rate.

Russo E, et al. Diabetes Metab Syndr Obes. 2013; 6: 161–170.

Diabetic Medications in CKD

Is It INSULINE ONLY OPTION?

Insulin regimens are the most commonly used to control glycemia in CKD

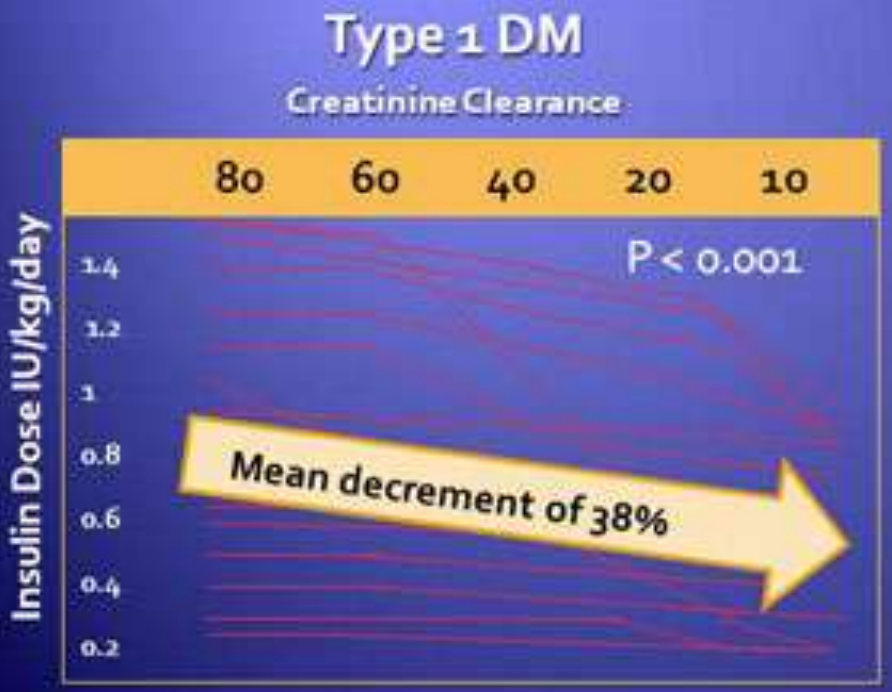
increasing half-life of insulin as CKD progresses, the risk for hypoglycemia increases.

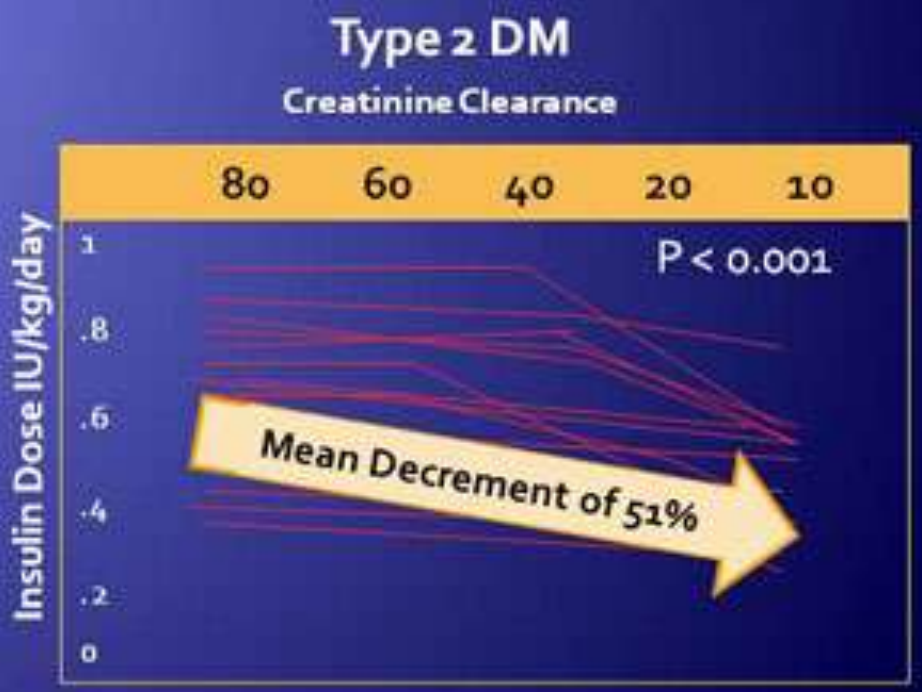
Insulin requirements decrease further in HD patients, particularly in those with residual diuresis (<500 ml/day),

- **Insulin requirement often decreases by 30%**

Declining Kidney Function = Declining Insulin Requirement

The insulin requirement of patients with Type 1 and Type 2 diabetes was found to be reduced as creatinine clearance rate declined. However, there was considerable inter-individual variation.

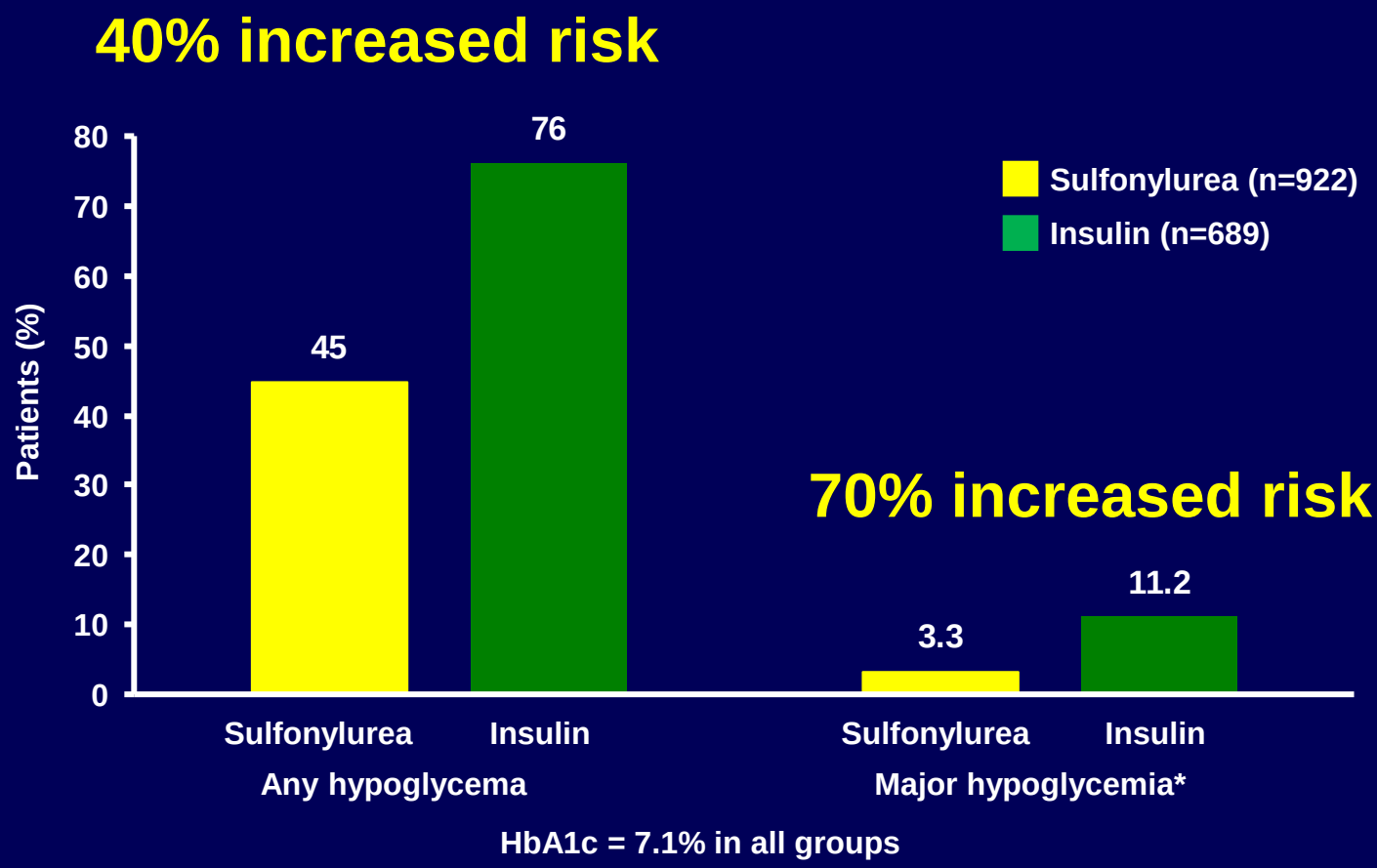




Adapted from Biesenbach G, et al. *Diabet Med*. 2003;20:642-645.

The risk of hypoglycemia with Insulin limits its effectiveness

Cumulative Incidence of Hypoglycemia in T2DM over 6 Years in UKPDS



HbA1c = 7.1% in all groups

SUs=sulfonylureas; T2DM=type 2 diabetes melllitus; *Requiring medical assistance or hospital admission

UK Prospective Diabetes Study Group. Diabetes.1995;44:1249–1258.

ADA & EASD 2012 Management of Other Co-Morbid Conditions With Diabetes

- Coronary Disease
- Heart Failure
- **Renal disease** ⟶
- Liver dysfunction
- Hypoglycemia

- Increased risk of hypoglycemia
- Metformin & lactic acidosis
  - US: stop @SCr ≥ 1.5 (1.4 women)
  - UK: half-dose @GFR < 45 & stop @GFR < 30
- Caution with SUs (esp. glyburide)
- **DPP-4-i's – dose adjust for most**
- Avoid exenatide if GFR < 30

Diabetes Care 2012;35:1364–1379
Diabetologia 2012;55:1577–1596

KDOQI Diabetes Guideline 2012:
DPP-4 Inhibitors Dose Adjustment in Renal Impairment Patients

DPP-4 inhibitor	
Sitagliptin	GFR >50 mL/min/1.73 m^2: 100 mg daily GFR 30-50 mL/min/1.73 m^2: 50 mg daily
Saxagliptin	GFR <30 mL/min/1.73 m^2: 25 mg daily GFR >50 mL/min/1.73 m^2: 5 mg daily GFR ≤50 mL/min/1.73 m^2: 2.5 mg daily
Linagliptin	No dose adjustment
Vildagliptin**	GFR ≥50 mL/min/1.73 m^2: 50 mg twice daily GFR <50 mL/min/1.73 m^2: 50 mg daily

National Kidney Foundation. KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 update. *Am J Kidney Dis*. 2012;60(5):850-886.

National Kidney Foundation® KDOQI

Vildagliptin renal safety has been assessed with 14.000 patient in meta- analysis of 38 clinical trails

And there is no increased risk of AEs and SAEs in patients with normal renal function and mild renal impairment with vildagliptin and other comparators (placebo, insulin and other OAD).

Ligueros-Saylan M, et al. *Diab Obes Metab* 2010 12:495-509

Safety is well established with vildagliptin with type 2 diabetic patients undergoing Hemodialysis

- **No serious adverse effects** such as hypoglycemia or liver impairment were observed in any patient.

- **Vildagliptin was effective as a treatment for diabetic patients undergoing HD.**

HD: Hemodialysis

Ito *et al.* Efficacy of vildagliptin in HD patients *Endocrine Journal 2011*, ***58 (11), 979-987***

Dipeptidyl Peptidase IV Inhibitor Attenuates Kidney Injury in Streptozotocin-Induced Diabetic Rats

Liu, et al J Pharmacol Exp Ther. 2012 ;340(2):248-55

Vildagliptin Attenuates Kidney Injury

Decrease

- **Proteinuria,**
- **Albuminuria,**
- **Urinary albumin/creatinine ratio,**
- **Serum creatinine,**

+

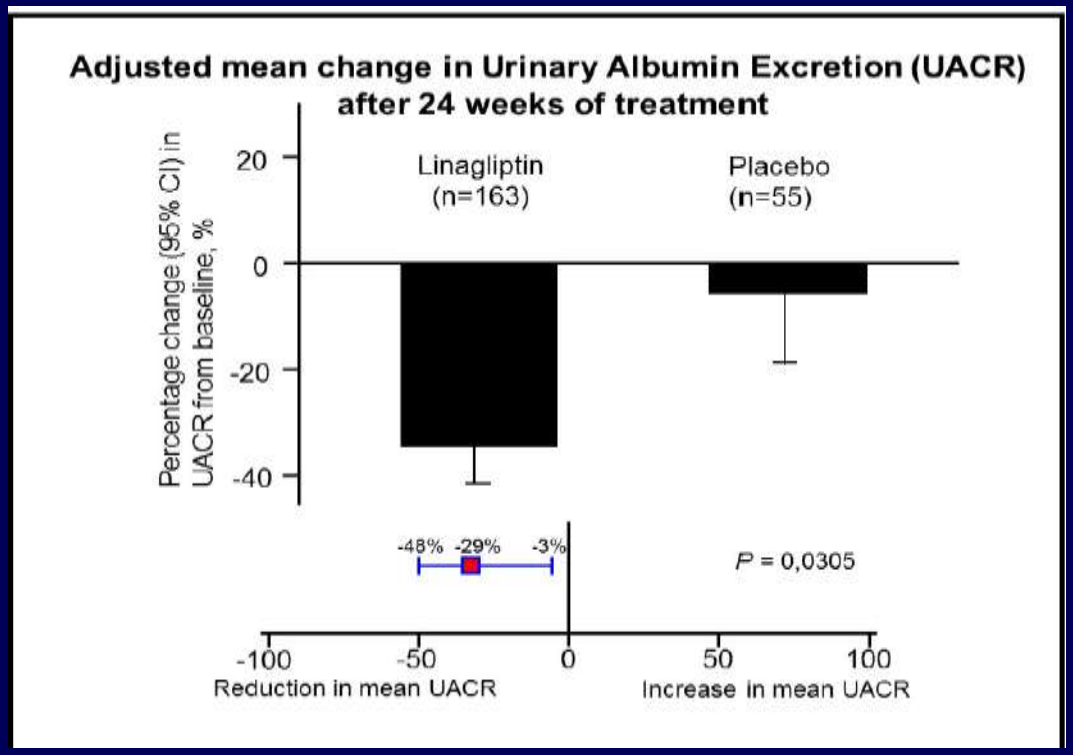
- **Improve creatinine clearance, and delay glomerular and tubulointerstitial fibrosis in diabetic rats**

Liu, et al J Pharmacol Exp Ther. 2012 ;340(2):248-55

" Novartis is not recommending indications outside the approved BPI in Egypt"

Anti-albuminuric Effect of DPP-4 Inhibitors in Patients with Overt Diabetic Nephropathy

- After 6 months exposure to DPP-4 inhibitors, statistically significant reductions in UACR versus placebo has been confirmed

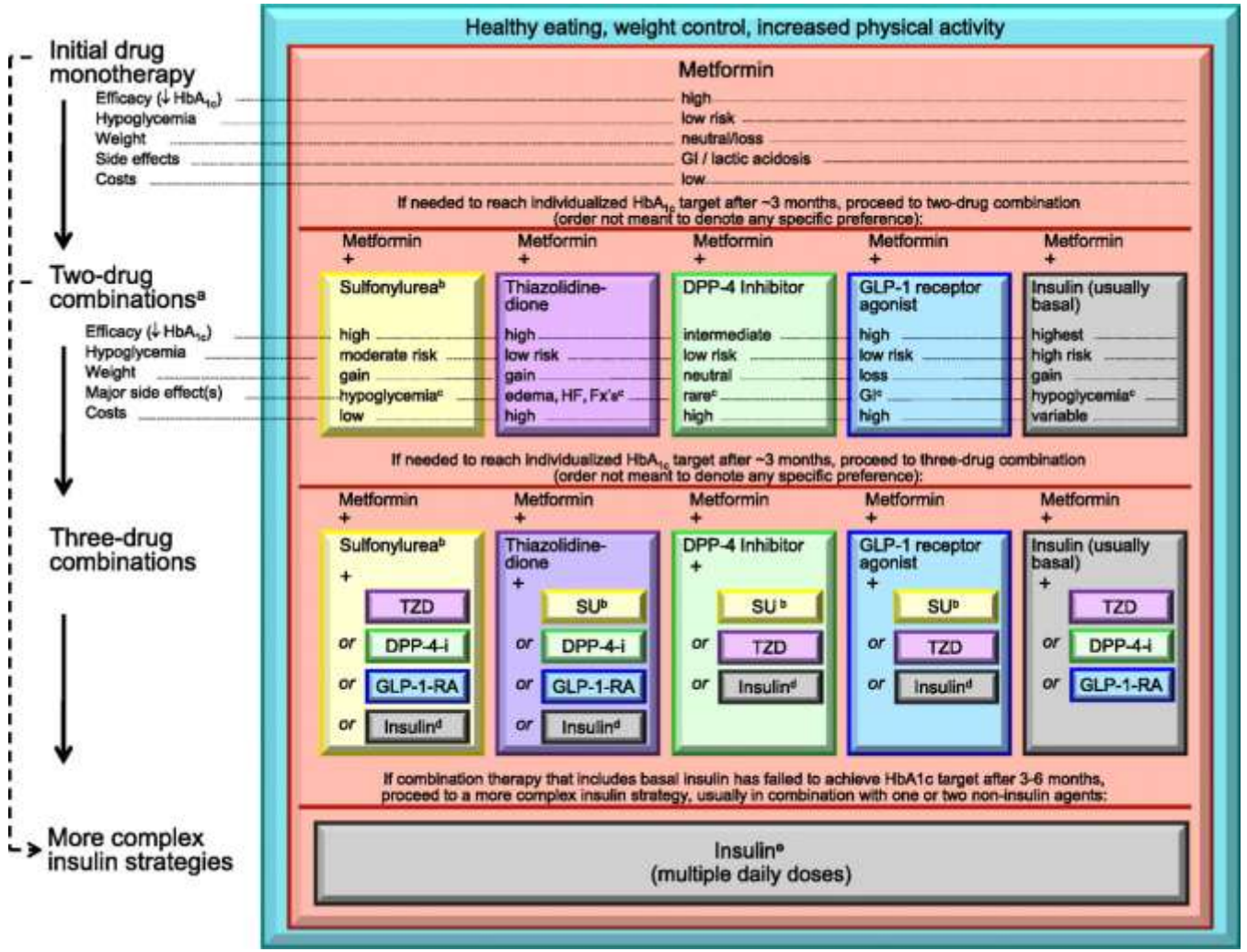


- Macro- and microalbuminuria are used to chart the progression of renal pathology.
- They are also predictive risk factors for non-fatal and fatal cardiovascular events in diabetic and non-diabetic patients.

UACR= urine albumin to creatinine ratio

Hocher et al , Kidney Blood Press Res 2012;36:65-84

Antihyperglycemic therapy in type 2 diabetes: general recommendations.



Inzucchi S E et al. Dia Care 2012;35:1364-1379

American Diabetes Association.


THANK YOU